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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,010	05/01/2001	Perry A. Frey	032026-0476D	5359

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FOLEY & LARDNER
150 EAST GILMAN STREET
P.O. BOX 1497
MADISON, WI 53701-1497

EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,010	FREY ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32 and 36-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *29,30,32 and 37-45* is/are rejected.

7)☐ Claim(s) *31,36 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants amendment of claims 29, 31, 36, 41 and 46, Paper No. 10, 4/30/2003, is acknowledged. Claims 29-32, and 36-46 are still at issue and are present for examination.

Applicants' arguments filed on 4/30/2003, Paper No. 10, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

Applicants filing of information disclosures, Paper No. 11, filed 4/30/2003, is acknowledged. Those references considered have been initialed.

Claim Objections

Claims 31, 36, 46 are objected to because of the following informalities:

Claims 31, 36 and 46 are dependent from rejected claims 30, 29, and 37 respectively.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of claims 39 and 45 as being indefinite in that each is confusing in that they are each drawn to the method of producing L-β-lysine of claims 30 and 37, respectively, wherein the a number of cofactors are required for lysine 2,3-aminomutase activity is hereby withdrawn based on applicants arguments presented in Paper No. 10, 4/30/2003.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 30, 32, 37-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was originally stated in the previous office action. In response to this rejection applicants have amended claims 29, 31, 36, 41 and 46 and traverse this rejection as it applies to the amended claims. It is noted to applicants that the current claim set is rejected under 112 1st paragraph as lacking adequate written description, not for a lack of enablement and applicants should argue the rejection as such.

Applicants traverse this rejection on the basis that they disagree with the characterization of the invention. Applicants argue that the amendment of claim 29 to recite the use of a prokaryotic host cell is clearly supported by the specification, as are methods of expression of proteins in prokaryotic hosts, suitable vectors and techniques.

Applicants further argue that claim 30 is also definite and patentable because applicants disclosure teaches sufficient representative examples of lysine 2,3-aminomutase and methods to obtain any purified lysine 2,3-aminomutase. Applicants argue that applicants are not claiming all possible DNA sequences of lysine 2,3-aminomutase, but rather applicants are claiming a method for producing L-β-lysine which uses any purified lysine 2,3-aminomutase and that applicants disclosure supports this claim because applicants teach "the present invention contemplates the use of Clostridial enzyme sequences to identify lysine 2,3-aminomutase from other species and applicants contemplates variants of such 2,3-aminomutases and the use of such enzymes to prepare β-lysine.

Applicants argument is not found persuasive because as was previously stated, claims 29, 30, 32, 37-45 are directed to all possible methods of producing L-β-lysine comprising culturing any prokaryotic host cell comprising any expression vector that encodes any lysine 2, 3-aminomutase in the presence of L-lysine (claims 29, 37, 42, 43, 44, 45), incubating L-lysine in the presence of any lysine 2, 3-aminomutase (claim 30, 32, 38, 39) or contacting L-lysine with any lysine 2, 3-aminomutase immobilized on a suitable support (claims 40, 41).

The specification, however, only provides the representative species of the claimed methods comprising the use of the lysine 2,3-aminomutase enzymes of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, and 16 and the DNAs which encode them, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification fails to describe additional

representative species of the enzymes, used by the methods, by any identifying structural characteristics or properties other than by their amino acid sequences and activity, for which no predictability of structure is apparent. The mere contemplation of lysine 2,3-aminomutase from other species and as well as variants of such lysine 2,3-aminomutases and the use of such enzymes to prepare β-lysine, does not sufficiently describe the claimed genus of methods of use of any protein having lysine 2, 3-aminomutase activity. Applicants disclosure of the species of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, and 16 does not put applicants in possession of all possible lysine 2,3-aminomutases and thus applicants were not in possession of the claimed methods of use of all possible lysine 2,3-aminomutases.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30, 38 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Chirpich et al. (J. Biol. Chem. Vol. 245, No. 7, pp. 1778-1789, 1970, See IDS).

Chirpich et al. teach the purification of lysine 2,3-aminomutase from *Clostridium* SB4 and a method of producing L-β-lysine comprising incubating L-lysine in a solution containing purified lysine 2,3-aminomutase and the cofactors required for lysine 2,3-aminomutase activity followed by isolating L-β-lysine from the incubation solution (see pages 1779-1780, *Enzyme Activation Assay*).

Claims 30, 38 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Chirpich et al. (Preparative Biochemistry. Vol. 3, No. 1, pp. 47-52, 1973, See PTO-892, ref U).

Chirpich et al. teach the preparation of L-β-lysine from L-lysine comprising incubating L-lysine in a solution containing lysine 2,3-aminomutase from lysine-fermenting clostridia followed by the isolation/separation of L-b-lysine by differential elution. As the preparation yielded 123 millimoles or 61% based on the initial amount of lysine all cofactors required for lysine 2,3-aminomutase activity were present for the reaction.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29, 37, 42, 43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chirpich et al. (J. Biol. Chem. Vol. 245, No. 7, pp. 1778-1789, 1970, See IDS).

As discussed above, Chirpich et al. teach the purification of lysine 2,3-aminomutase from *Clostridium* SB4 and a method of producing L-β-lysine comprising incubating L-lysine in a solution containing purified lysine 2,3-aminomutase and the cofactors required for lysine 2,3-aminomutase activity followed by isolating L-β-lysine from the incubation solution (see pages 1779-1780, *Enzyme Activation Assay*). Chirpich et al. teach that their purification method is more effective than that which was previously reported.

One of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 to generate antibodies against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for further use in the recombinant production and characterization of lysine 2,3-aminomutase. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Any method of recombinantly expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by

Chirpich et al., which would involve the isolation of L-β-lysine from the cultured cells. The reasonable expectation of success comes from the high degree of knowledge in the art with respect to the isolation and recombinant expression of the genes which encode previously isolated proteins as well as the teachings of the isolation of the lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al.

Claims 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chirpich et al. (J. Biol. Chem. Vol. 245, No. 7, pp. 1778-1789, 1970, See IDS) as applied to claims 29, 37, 42, 43 and 45 above, further in view of Rozzell (U.S. Patent No. 4,88,0738), and Kusumoto et al. (Tetrahedron Letters, Vol 23, No. 29, pp 2961-2964).

As discussed above, Chirpich et al. teach the purification of lysine 2,3-aminomutase from *Clostridium* SB4 and a method of producing L-β-lysine comprising incubating L-lysine in a solution containing purified lysine 2,3-aminomutase and the cofactors required for lysine 2,3-aminomutase activity followed by isolating L-β-lysine from the incubation solution (see pages 1779-1780, *Enzyme Activation Assay*). Chirpich et al. teach that their purification method is more effective than that which was previously reported.

Kusumoto et al. teach the synthesis of the antibiotic streptothricin F comprising adding β-lysine, carbamoyl and streptolidine moieties to the gulosamine molecule. Kusumoto et al. further teach that this synthesis method makes it possible to synthesize structural analogs of streptothricin which are necessary for the future studies of the relationship between structure and activity of the streptothricin antibiotic.

Rozzell teaches the biocatalytic methods for producing a desired amino acid using purified or partially purified enzymes either in solution or as immobilized enzymes.

One of ordinary skill in the art at the time of filing would have been motivated to use the purified lysine 2,3-aminomutase from *Clostridium* SB4 as taught by Chirpich et al., to generate antibodies against the enzyme such that the nucleic acid which encodes the enzyme could be isolated for use in the recombinant production lysine 2,3-aminomutase. One would have been further motivated to immobilize the recombinantly expressed lysine 2,3-aminomutase for use in a method of producing L-β lysine for use in the synthesis of the antibiotic streptothricin and streptothricin analogs, so that the enzyme could be used repeatedly in a process of synthesizing L-β-lysine. Further it is known in the art that enzyme immobilization is a means of stabilizing the enzyme and thus increasing the amount of L-β-lysine that is produced per lysine 2,3-aminomutase molecule/protein. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. Any method of recombinantly expressing the lysine 2,3-aminomutase from *Clostridium* SB4 would further involve an activity assay as taught by Chirpich et al. which would involve the isolation of L-β-lysine from the cultured cells. The reasonable expectation of success comes from the high degree of knowledge in the

art with respect to the isolation and recombinant expression of the genes which encode previously isolated proteins.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
July 11, 2003